86042103 B3 D21 E13

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [4]: C07D 239/02, 239/70	A1	(11) International Publication Number: WO 86/ 00616
		(43) International Publication Date: 30 January 1986 (30.01.86)

(21) International Application Number: PCT/US85/01329

(22) International Filing Date: 15 July 1985 (15.07.85)

(31) Priority Application Numbers: 630,639
727,357

(32) Priority Dates: 13 July 1984 (13.07.84)
25 April 1985 (25.04.85)

(33) Priority Country: US

(60) Parent Application or Grant
(63) Related by Continuation
US 630,639 (CIP)
Filed on 13 July 1984 (13.07.84)

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(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.
With amended claims.

(54) Title: SUBSTITUTED PYRIMIDINE OXIDES USEFUL FOR HAIR GROWTH PROMOTION

(57) Abstract

Novel substituted pyrimidine oxides and their salts and use of these in combination with retinoids and/or prostacyclin analogues to increase the rate of hair growth and to prolong the anagen phase of the hair cycle and to treat certain types of alopecias. The unexpected novel advantages to be gained from the use of the instant invention are: improved solubility and improved stability of active compounds through increased dispersion of charge; longer action of compounds; excellent penetration of skin due to the lipophilic substituents; and compatibility of compounds with non-polar solvents useful for the preservation of the polar groups while in contact with the skin and useful for the encapsulation of the compounds within a syneresis-free hydrophobic polymeric network.

NEW 2,6-BIS: ACYLAMINO-4-AMINO-PYRIMIDINE $\overset{=}{N}$-OXIDE CDS. + AND SULPHOXY DERIVS., USEFUL FOR PROMOTING GROWTH OF HAIR

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Substituted Pyrimidine Oxides Useful for Hair Growth Promotion

Brief Summary of the Invention

Novel substituted diamino pyrimidine oxides and their salts, processes for preparing the compounds as well as the preferred mode of applying the compounds are described. These compounds are used to increase the rate of hair growth and prolong the anagen phase of the hair cycle and as peripheral vasodilators.

Cross References to Related Applications

This application is related in part to application serial U.S. 235,169, filed February 17, 1981; application serial U.S. 318,697, filed November 9, 1981; application serial U.S. 386,730 filed June 9, 1982, and application serial U.S. 414,854 filed September 3, 1982, and patents listed as follows: German Offec. 2,804,518 filed August 17, 1978; U.S. Patents 4,220,772 and 4,256,886; German Offen. 2,804,519 filed August 10, 1978; Swiss Applic. 78/7,910 filed July 21, 1978: H tica Chimica Acta Vol. 65 Fasc. 5 (1983), pp. 669-672: U.S. Patents 4,150,131 and 4,360,521 and Belgium Patent No. 893,333 filed January 14, 1983 and CH application 81/4,640 filed July 15, 1981, as well as U.S. Pat. Nos. 3,461,461, 3,382,248, 3,973,016, 4,287,338, 3,464,987 and the British Patent No. 1,486,682.

Background of the Invention:

Minoxidil, a 2,4 diamino 6 piperidino pyrimidine-3-oxide is known in the art as an antihypertensive. U.S. Patent 4,139,619, to Chidsey, describes the use of minoxidil and derivatives as hair growth promoters.

PCT application U.S. 85/00556 by G. Bazzano, describes the use of substituted pyrimidine-oxides for hair growth promotion, particularly carbamate derivatives, and oxadiazolopyrimidine carbamates.

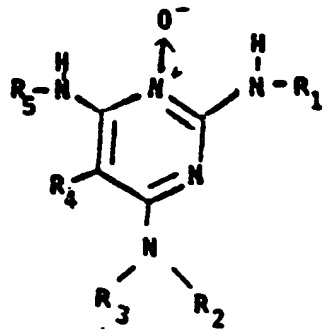
It is the purpose of the present invention to provide additional compounds which overcome some of the problems inherent in the use of previously described compounds.

The compounds of this invention afford the following advantages: improved solubility, and improved stability of active compounds through in-

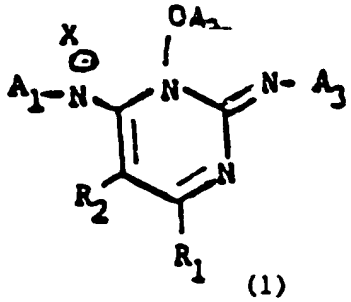
creased dispersion of charge; longer action of compounds; excellent penetration of skin due to the lipophilic substituents; and compatibility of compounds with non-polar solvents useful for the preservation of the polar groups, while in contact with the skin and useful for the encapsulation of the compounds within a syneresis-free hydrophobic polymeric network.

Field of the Invention:

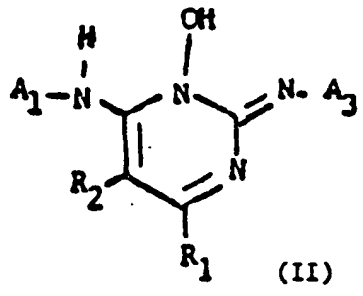
This invention relates to compositions of matter and to methods for producing them, their use and their application. In particular, this invention relates to novel substituted diamino pyrimidine oxides and their salts of the general formula:



More specific salt forms of this compound could be written as follows:



(I)



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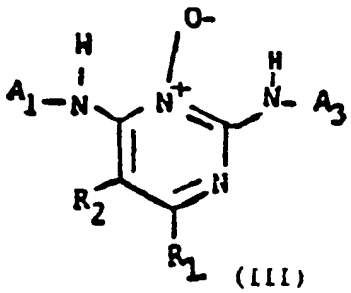

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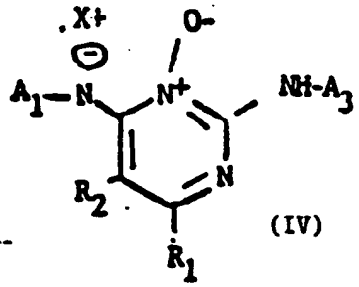

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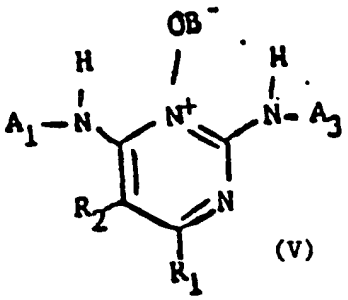


(V)

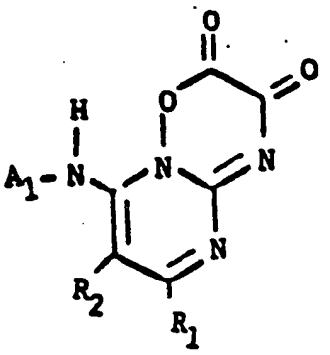
wherein, in Formulas I through V, R_1 is a moiety selected from the group consisting of substituents of the formula;

wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, with the proviso that both R_3 and R_4 are not hydrogen, and the heterocyclic functionality systems, N-aziridinyl, N-piperidinyl, N-azetidinyl, N-pyrrolidinyl, hexahydro-1H-azepin-1-yl, 4-alkylpiperazinyl, hexahydro-1(2H)-azocinyl, (wherein the alkyl portion of the moiety is of one to 3 carbon atoms), 4-morpholinyl, 4-thiomorpholinyl, 3,6-dihydro-1(2H)-pyridinyl, 3-pyrrolindyl, 2,3,4,7-tetrahydro-1H-azepine-1-yl, and 3,4,7,8-tetrahydro-1(2H)-azocinyl, each of said heterocyclic groups having attached as substituents on carbon atoms thereof zero to 3 lower alkyls, inclusive, a nitrogen atom of each of said heterocyclic moieties being the point of attachment of R_1 to the ring in said formula. When R_1 is $N-R_3R_4$, R_3 and R_4 can be alike or different. When R_1 is a heterocyclic moiety, the alkyls which can be attached thereto can all be different, or any two or all of them can be alike.

In Formulas I - V, R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkaralkyl, lower alkoxyaralkyl, and lower haloaralkyl. In Formulas I - V, R_2 can also be selected from the group consisting of chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower alkylphenylthio, and halphenylthio. In Formulas I - V, R_2 can also be assigned in accordance, with the definition applied for R_1, above. R_1 and R_2 may be the same within the scope of that definition.

(4)

Precursors of Formulas I - V compounds can be the following:



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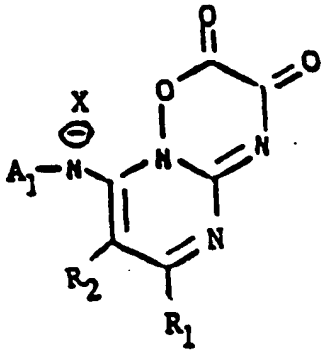


VII.

wherein, in each instance, R_1 is as defined above.

In Formulas VI and VII, R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaralkyl, lower alkaralkyl, lower alkoxyaralkyl, and lower haloaralkyl. In Formulas VI and VII, R_2 can be selected from the group consisting of chlorine, bromine, iodine, nitroso, nitro, amino, phenylthio, lower alkylphenyithio, and halophenylthio. In Formulas VI and VII, R_2 is assigned the same definition as R_1, above. R_2 can be the same as or different than R_1 within the scope of that definition.

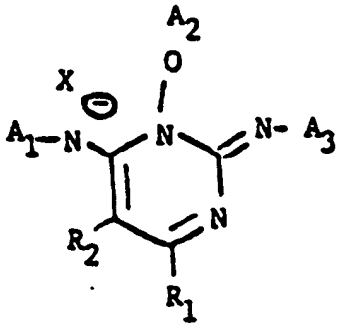
Examples of lower alkyl are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, ocyl and isomeric forms thereof. Examples of lower alkenyl are allyl, 1-methylallyl, 2-methylallyl (methallyl), 2-butenyl (crotyl), 3-butenyl, 1,2-dimethylallyl, 1-dimethylallyl, 2-thylallyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 3-pentenyl, 2,3-dimethyl-2-butenyl, 1, 1, 2-trimethylallyl, 1, 3-dimethyl-2-butenyl, 1-ethyl-2-butenyl, 4-methyl-2-petenyl, 2-ethyl-2-pentenyl, 4, 4-dimethyl-2-pentenyl, 2-heptenyl, 2-octenyl, 5-octenyl, 1, 4-dimethyl, 4-hexenyl, and the like. Examples of lower alkoxyalkyl are 2-methoxyethyl, 2-ethoxyethyl, 2-butoxyethyl, 2-hexyloxyethyl, 2-octyloxyethyl, 2-methoxypropyl, 3-methoxypropyl, 3-propoxypropyl, 2-methoxybutyl, 3-ethoxybutyl, 4-butoxybutyl, 2-ethoxyhexy,, 3-methoxy-3-methylpentyl, 4-methoxyoctyl, and the like. Examples of lower cycloalkyl are cyclopropyl, 2-methylcyclopropyl, 2, 2-dimethylcyclopropyl, 2,3-diethyl-cyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, 2, 3, 4-trihylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, 3-pentylcyclopentyl, 3-tert-butylcyclopentyl, cyclohexyl,

4-tert-butylcyclobexyl, 3-isopropylcyclohexyl, 2, 2-dimethylcyclohexyl, cycloheptyl, cycoctyl, and the like. Examples of lower aryl are phenyl, 1-naphtyl, and 2-naphthyl. Examples of lower alkaryl are o-tolyl, m-tolyl, p-tolyl, methylphenyl, p-tert butylphenyl, the isomeric forms of xylyl, the isomeric forms of trimethylphenyl, 4-methyl-1-naphthyl, 6-propyl-2-naphthyl, 2, 4, 5, 7-tetramethyl-1-naphthyl, and the like. Examples of lower aralkyl are benzyl, phenethyl, 1-phenylethyl, 2-phenylpropyl, 4-phenylbutyl, 6-phenylhexyl, 5-phenyl-2-methylpentyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-napthyl) ethyl and the like. Examples of lower alkaralkyl are o-tolylmethyl, m-tolyl-methyl, p-tolylmethyl, 4-tert-butylphenylmethyl, 2-(p-tolyl)ethyl, 1-(m-tolyl)ethyl, 3-(o-ethylphenyl)propyl, 4-methyl-1-naphthylmethyl, 6-tert-butyl-2-naphthylmethyl, and the like. Examples of lower alkoxyaralkyl are o-methoxybenzyl, m-methoxybenzyl, p-methoxybenzyl, 2-(m-methoxyphenyl)ethyl,3-(p-ethoxyphenyl)propyl, 4-(p-tert-butoxyphenyl) butyl, 4-methoxyl-1-naphthylmethyl, and the like. Examples of lower haloaralkyl are o-chloro-benzyl, m-fluorobenzyl, p-bromobenzyl, 2-(m-iodophenyl)ethyl, 2,4-dicloro-benzyl, 6-bromo-1-naphthylmethyl, 4-p-chlorophenyl)butyl and the like. Examples of lower alkylphenylthic are o-tolylthio, p-tolylthio, the isomeric forms of xylylthio, p-ethylphenylthio, m-butylphenylthio and the like. Examples of halophenylthio are p-chlorophenylthio, m-bromophenylthio, o-fluorophenylthio, 3,4-dichlorophenylthio and the like.

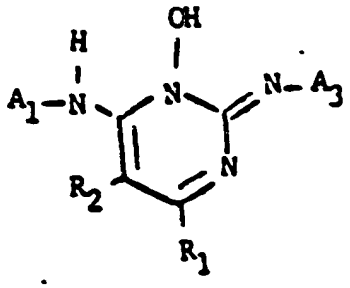
Examples of heterocyclic moieties within the scope of R_1 in addition to those already mentioned above, are 2-methylaziridinyl, 2-ethylaziridinyl, 2-butylazirindinyl, 2,3-dimethylaziridinyl, 2, 2-dimethylaziridinyl, 2-methylazetidinyl, 3-methylazetininyl, 2-octylazetidinyl, 2,2-dimethylazetidinyl, 3,3-diethylazetidinyl, 2, 4, 4-trimethylazetidinyl, 2, 3, 4-trimethylazetidinyl, 2-methylpyrrolidinyl, 3-butylpyrrolidinyl, 2-isohexylpyrrolidinyl, 2, 3-dimethyl-pyrrolidinyl,2, 2-dimethylpyrrolidinyl, 2,5-diethylpyrrolidinyl, 3-tert-butyl-pyrrolidinyl, 2,3,5-trimethylpyrrolidinyl, 3,4-dioctylpyrrolidinyl, 2-methyl-piperidino, 3-methylpiperidino, 4-methylpiperidino, 3-isopropylpiperidino, 4-tert-butylpiperidino, 2-methyl-5-ethylpiperidino, 3, 5-dipentylpiperidino, 2, 4, 6-trimethylpiperidino, 2, 6-dimethyl-4-octylpiperidino, 2, 3, 5-triethyl-piperidino, 2-ethylhexahydroazepinyl, 4-tert-butylhexalhydroazepinyl, 3-heptylhexa-hydroazepinyl, 2, 4-dimethylhexahydroazepinyl, 3, 3-dimethylhexahydroazepinyl, 2, 4, 6-tripropylhexahydro-

azepinyl, 2-methylheptamethylenimino, 5-butylheptamethylenimino, 2, 4-diisopropylheptamethylenimino, 3, 3-diethylheptamethylenimino, 2, 5, 8-trimethylheptamethylenimino, 3-methyloctamethylenimino, 2, 9-diethyloctamethylenimino, 4-isooctyloctamethylenimino, 2-ethylmorpholino, 2-methyl-5-ethylmorpholino, 3, 3-dimethylmorpholino, 2, 6-ditert-butylmorpholino, 4-methylpiperazinyl, 4-isopropylpiperazinyl and the like. In each of the above examples of heterocyclic moieties, the free valence and hence the point of attachment to a carbon atom of the pyrimidine ring, is at the heterocyclic nitrogen atom.

In the novel Formulas I through V substituents B and X can be salts or A_1, A_2 and A_3 represent amides derived by acylation. These can be formed from Ethyl oxallyl chloride or ethyl chloroformate or carboxylic acid anhydrides, carboxylic acid chlorides, as well as Ketene. The compounds can be single compounds or mixtures of compounds depending on such factors as the nature of the reactants and the intermediates or the salts or the acylating agents, and the reaction conditions.



I



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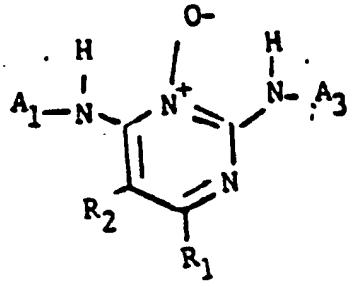

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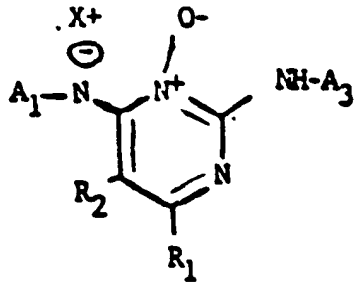

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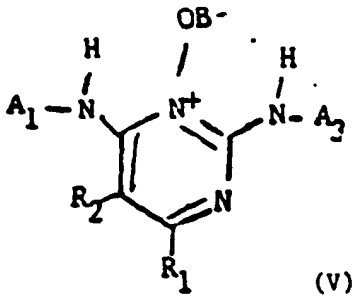


(V)

Although substantially any acylating agent can be used to produce these acylates, especially suitable are acylating agents derived from alkanoic (including half-acid chlorides of dibasic examples) as well as the anhydrides, mixed anhydrides and acid chlorides of alkanoic, cycloalkanoic, alkenoic, cycloalkenoic, aralkanoic, aromatic and heterocylic carboxylic acids.. These anhydrides and acid chlorides can also be substituted on any carbon, but the carbonyl carbon with any of a wide variety of atomic or molecular moieties unreactive with the dihydropyrimidine reactants. Examples of such substituents are alkyl; e.g., methylthio, propylthio, heptylthio; dialkylamino; e.g., dimethylamino, diethylamino, dihexylamino; alkoxycarbonyl; e.g., methoxycarbonyl, propoxycarbonyl, nonoxycarbonyl; carboxyacyl; e.g., acetyl, butyryl; carboxamido; e.g., benzmido, acetamido; nitro, fluoro; cyano; and the like. Chlorine, bromine and iodine can also be substituents on aromatic portions of the acylating agents.

Examples of suitable anhydrides are acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride, acrylic anhydride, crotonic anhydride, cyclohexane carboxylic anhydride, benzoic anhydride, naphthoic anhydride, furoic anhydride and the like, as well as the corresponding anhydrides substituted with one or more of the above-mentioned substituents. Examples of suitable acid chlorides are acetyl chloride, propionyl chloride, crotonyl chloride, cyclohexanecarbonyl chloride, 3-cyclohexenecarbonyl chloride, phenylacetyl chloride, succinoyl chloride benzoyl chloride, naphthoyl chloride; furoyl chloride, 3-pyridinecarbonyl chloride, phthaloyl chloride and the like, as well as the corresponding acid chlorides substituted with one or more of the above mentioned substituents.

One molecular equivalent of an acylating agent should be used for the introduction of each acyl moiety. When a reactive acylating agent such as ethyl oxalyl chloride is used with heating, a cyclized compound is usually obtained. These compounds can be hydrolyzed to the bis or mono acylates.

The acylation usually takes place rapidly in the range of -20°C to about +50°C. Suitable diluents are CH_2Cl_2; or, diethyl ether and tetrahydrofuran; ketones; e.g. acetone and methyl ethyl ketone; esters; e.g.

methyl acetate and ethyl acetate; acetonitrile; pyridine and the like. The desired acylated product often present from the reaction mixture in crystalline form can be separated in the usual manner; for example, by filtration or centrifugation. Alternately, the diluent can be evaporated, preferably at reduced pressure. The acylates can be purified by conventional techniques; for example, by recrystallization from a suitable solvent or mixture of solvents.

Example Page

Further Examples of Acyl Derivatives

Alkoxyacyl Derivatives (Carbamates)

A_1 - -C(=O)-O-methyl
-C(=O)-O-ethyl
-C(=O)-O-butyl
-C(=O)-O-i-butyl
-C(=O)-O-benzyl
-C(=O)-O-2-methoxy-ethyl

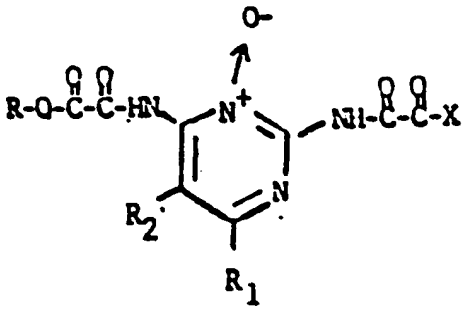
Alkoxyoxalyl Derivatives (Oxamates) or (Oxoacetates)

or A_1 -C(=O)-C(=O)-O-methyl
-C(=O)-C(=O)-O-ethyl
-C(=O)-C(=O)-O-butyl
-C(=O)-C(=O)-O-i-butyl
-C(=O)-C(=O)-O-benzyl
-C(=O)-C(=O)-O-2-methoxy-ethyl

The acylates can form salts. The Formula IV through VII compounds can be salts when the cation is (X), represented by protonated primary, secondary or tertiary amines . The amine compounds can be aliphatic and alicyclic in structure. The aromatic and heteroaromatic amines can be substituted or unsubstituted . The cation can be donated by any base stronger than an amine such as NaOH, barium hydroxide, etc. Where the bases constitute primary, secondary and tertiary amines or any base strong enough to remove the hydrogen on the activated urethane group in position 4.

The amines referred to above can be represented by the formulas: [1°] R_1NH_2 [2°] R_1R_2NH [3°] $R_1R_2R_3N$ The R groups can be aliphatic and alicyclic amines, aromatic and heteroaromatic amines can also be used.

The novel compounds of Formulas I through V can also form the following carboxy derivatives:



I

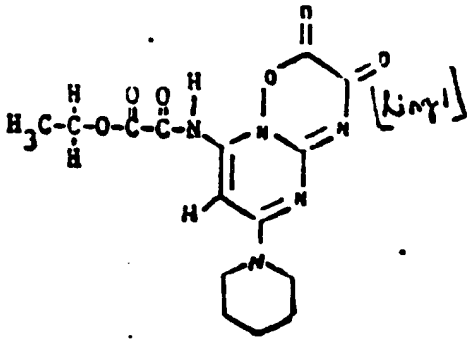
The X in the above Formula I can be represented by the following:
X=OR where R can be H or CH_3 or any alkyl group or phenyl or other aromatic group or heterocylic group.

X = NR_1R_2 where R_1=R_2=H

X = S-R where R is defined as R_1 or R_2 above.

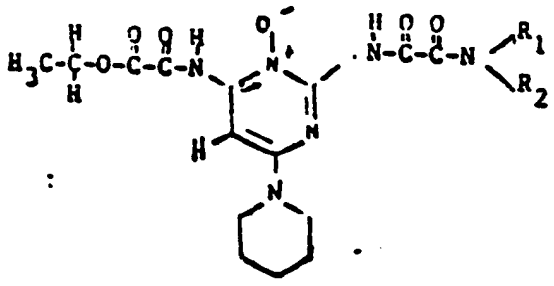
R_1 = CH_3 or alkyl group or aromatic or heterocylic group. R_2 can be the same or different from R_1.

Product A



The oxadiazino ring - Product A was opened by treating Product A in base with R_1R_2NH for 30 minutes. The resultant Product B is shown below:

Product B



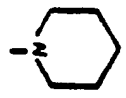
Product B when treated with strong bases yields the product shown-

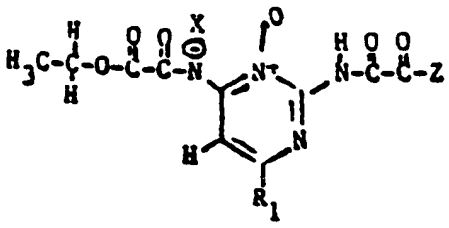
If the base is NaOH then X will be Na+

if the base is KOH then X will be K+

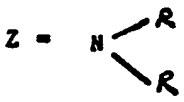
if the base is NH_4OH then X will be NH_4

if the base is a primary, soecondary or tertiary amine then X will be:

NR_1, NR_1R_2 or 



Z in the above formula can be :

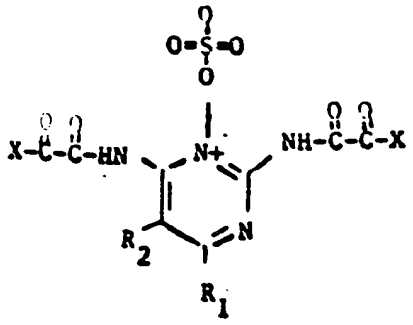


Z = S-R

The R's on constituent Z constitute symmetrically and unsymmetrically substituted saturated aliphatic, olefinic, acetylenic, alicyclic, substituted and unsubstituted aromatic and heterocylic groups.

The novel compounds of Formulas I through V can also form the following carboxy derivatives:

(Inner Salts)



II

The X in the above Formula II can be represented by the following:

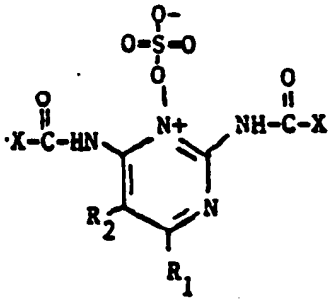
X = OR where R can be H or CH_3 or any alkyl group or phenyl or other aromatic group or heterocylic group.

X = NR_1R_2 where R_1 = R_2 = H

R_1 = CH_3 or alkyl group or aromatic or heterocyclic group. R_2 can be the same or different from R_1.

X = S-R where R is defined as R_1 or R_2 in the aforementioned.

The novel compounds of Formulas I through V can also form the following carboxy derivatives:



(Inner Salts)

III

The X in the above Formula III can be represented by the following:

X = OR where R can H or CH_3 or any alkyl group or phenyl or other aromatic group or heterocylic group.

X = NR_1R_2 where R_1 = R_2 = H

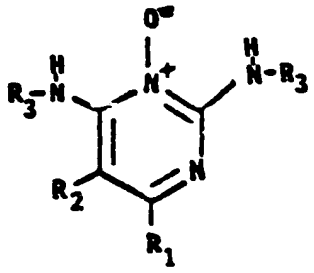
R_1 = CH_3 or alkyl group or aromatic or heterocylic group. R_2 can be the same or different from R_1

X = S-R where R is defined as R_1 or R_2 above.

Invention Technical Process Data

This invention relates to a method of preparing novel compounds of general formulas I and II.

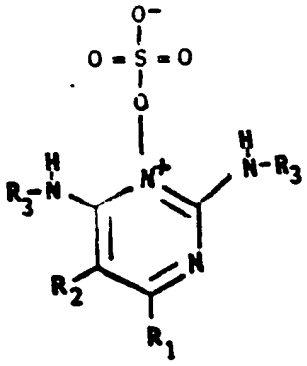
I



where R_3 is an alkyl oxalyl and R_1 is a heterocyclic moiety, or a substituted phenoxy group, or an O-Tosyl group, and R_2 is hydrogen.

In another aspect the process relates to compounds of the general Formula II, which comprises treating the compound of Formula I with a latent sulfate source such as sulfur trioxide pyridine complex, and sulfur trioxide triethyl amine complex.

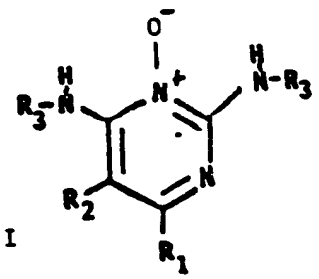
II



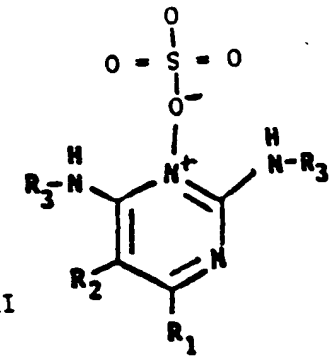
where R_2 is hydrogen, R_3 is carbamate or alkyl oxalyl and R_1 is the same as that described above.

Detailed Description of the Invention

The 4-[substituted]-2,6-bis(alkyl oxamyl)-pyrimidine-1-oxides and their corresponding inner salts, obtained according to the process of this invention, have the general Formula I and II, where R_3 is an



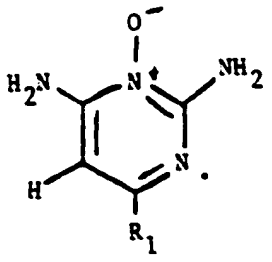
I



II

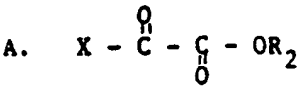
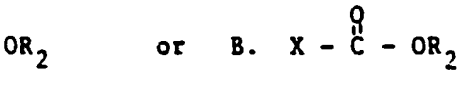
alkyl oxalyl or an alkoxy carbonyl. The term "alkyoxalyl" is used to define the RO-C-C group in which R constitutes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl and the like. The term "alkoxy carbonyl" is referred to RO-C in which R is the lower alkyl group. R_1 is a heterocyclic moiety containing nitrogen including tetrahydropyridine, piperidine, morpholine, pyrrolidine, thiomorpholine, diallylamine, or a substituted phenol such as p-cresol or an O-tosyl group.

According to the invention, derivatives of Formula I are prepared readily by reacting a compound of the Formula III, where R_1 is as previously described.



III

with an excess of an alkyl oxalyl halide of structure A, or with an excess of an alkyl halo formate, of structure B.

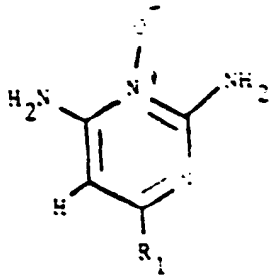
A.  or B. 

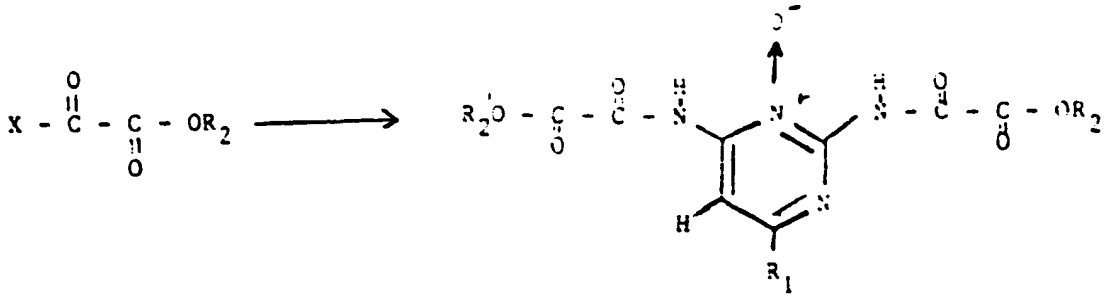
R_2 = lower alkyl X = Cl

in the presence of an amine such as pyridine or triethylamine.

Suitable solvents include chlorinated hydrocarbons, for example, methylene chloride and chloroform. The reaction is spontaneous and is conducted in the temperature range of 0-5°C. The reaction mixture is treated with an aqueous bicarbonate solution, for example, sodium bicarbonate and the two-phase system is then separated. The organic phase is dried and the final product is precipitated using non-polar solvents such as toluene and hexane. See Scheme 1:

Scheme 1



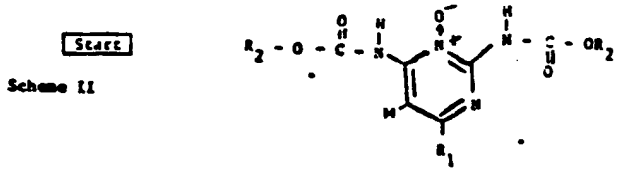


X, R_2 and R_1 are the same as previously mentioned

The majority of the oxamyl compounds have a bright yellow color and are somewhat light sensitive and may decompose to the parent compound on standing over a 6 month period in light on the laboratory shelf, in clear glass.

Another part of this invention deals with the synthesis, isolation and characterization of novel 4-[substituted]-2,6-bis (ethoxy carbonyl or alkoxy carbonyl amino)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt of Formula II.

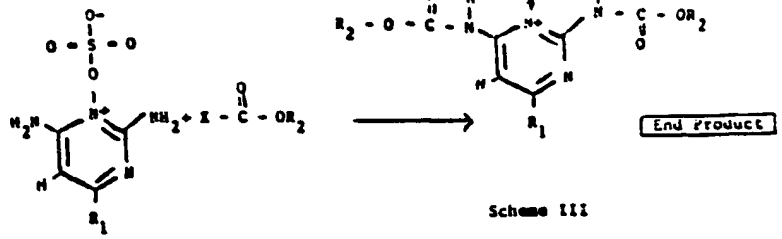
In general these compounds could be prepared by two different methods shown in Schemes II and III.



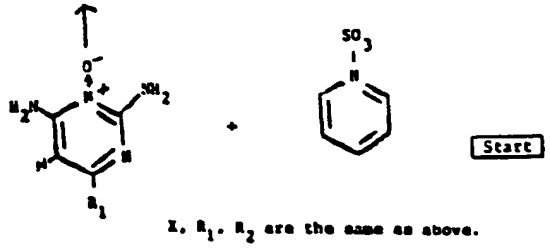
Scheme II

R_1 = piperidine, pyrrolidine, diallylamine, tetrahydro pyridine diethylamine

R_2 = lower alkyl, methyl, ethyl, etc.



Scheme III

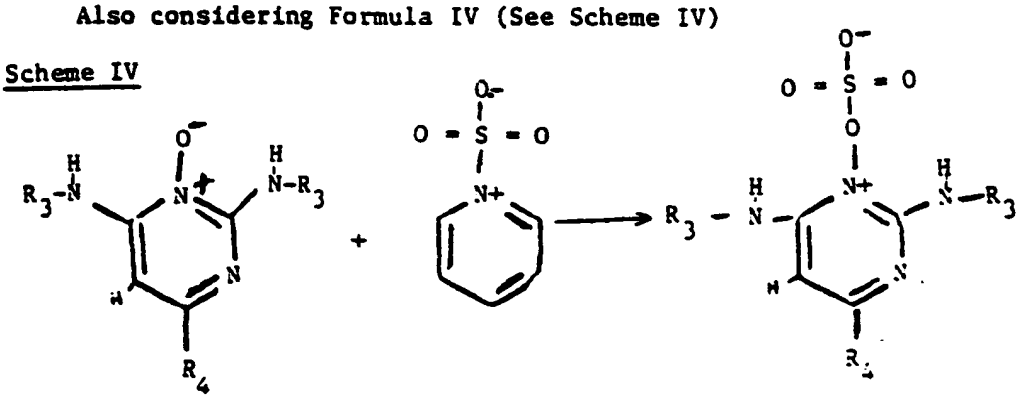


X, R_1, R_2 are the same as above.

In Method II (Scheme II) the novel 4-[substituted]-2,6-bis (alkyl oxalyl amino)-pyrimidine 3-oxides are treated at room temerature with sources of sulfur trioxide such as sulfur trioxide pyridine complex, or sulfur trioxide triethyl amine complex, in an inert solvent such as dimethyl formamide (DMF) or acetonitrile at room temperature. The sulfur trioxide reacts directly to form a sulfate with the substituted pyrimidine N-1 oxides, and is used in excess, usually in ratio of 1:2 or 1:1.5. Alternatively in Method III (see Scheme III) the 2,4-diamino-6-[substituted]-pyrimidine-3-oxide is converted to 2,6-diamino-4-[substituted-1-(sulfooxy) -pyrimidinium hydroxide, inner salt by a reaction with a latent sulfur trioxide source, which subsequently is treated with an alkyl oxalyl halide, preferably ethyl oxalyl chloride to yield the corresponding substituted pyrimidine-O-sulfates.

Also considering Formula IV (See Scheme IV)

Scheme IV



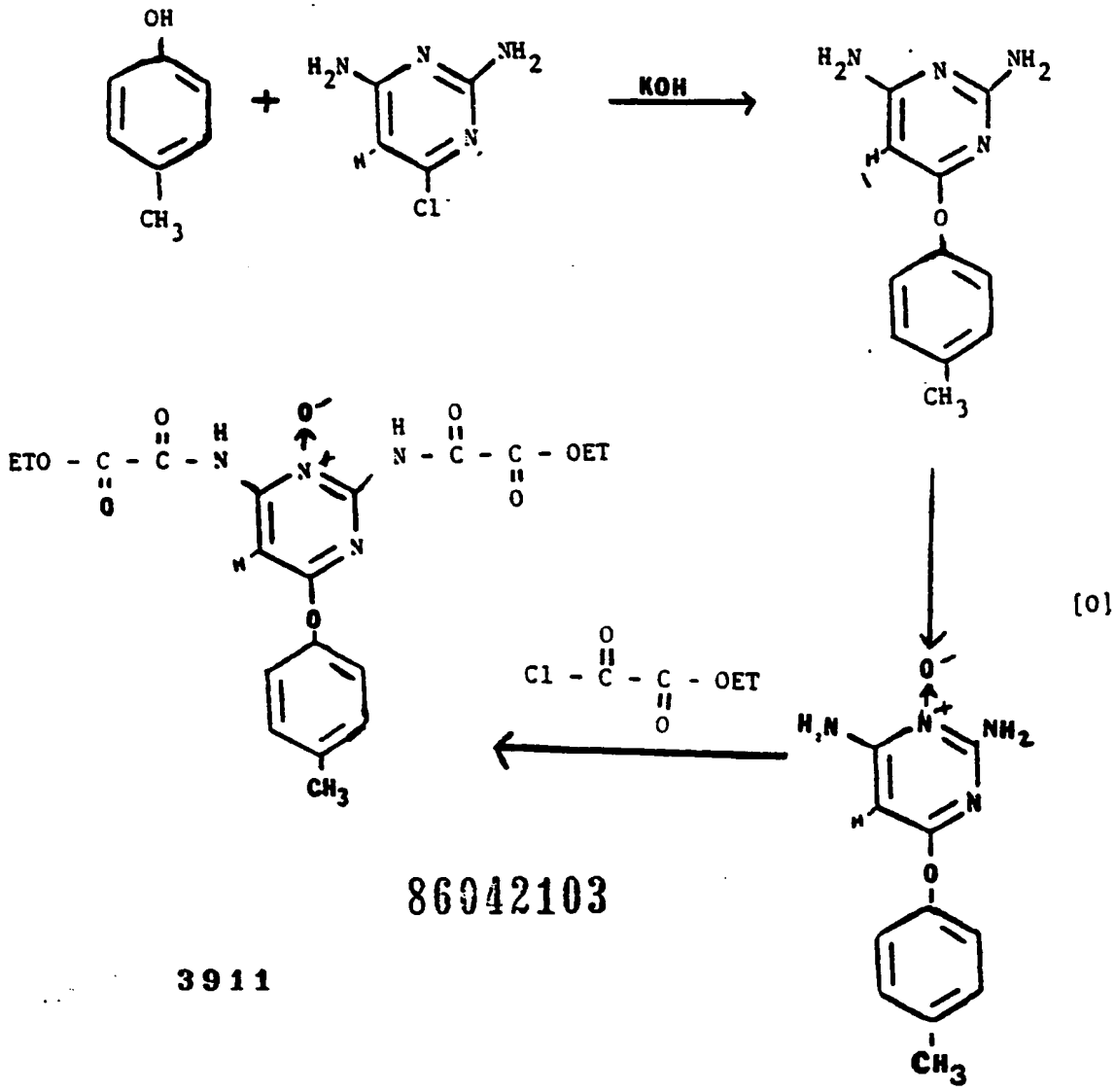
wherein R_3 is hydrogen, or methoxy, ethoxy, propoxy-carbonyl and R, is diallylamine, pyrrolidine, piperidine, tetrahydropyridine, morpholino or thiomorpholino. Example: The 4-(1,2,4,6-tetra hydro-1-pyridyl)-2,6-bis (ethoxy carbonyl amino)-pyrimidine-1-oxide (i.e., IV, R_3 is C_2H_5-O-C- and R_4 = 1,2,3,6-tetrahydro-pyridine) was reacted with sulfur trioxide pyridine complex in DMF at room temperature which afforded the 4-(1,2,3,6-tetra hydro-1-pyridyl)-2,6-bis(ethoxy carbonyl amino)-1-(sulfooxy) pyrimidinium hydroxide, inner salt.

This process must also include the preparation of the starting materials of Formula III, some of which have been claimed with a different method, in U.S. Patent 3,461,461, but surprisingly enough, no record of their syntheses and physical data is presented. These were all made and used as intermediate compounds in the invention of I and II.

Another novel compound, 2,4-diamino-6-(para-methyl-phenoxy) pyrimidine was synthesized by reacting p-cresol with 2,4-diamino-6-chloropyrimidine which was subsequently oxidized to 6-amino-4 (Para-methyl-phenoxy) 1,2-dihydro-1-hydroxy-2-amino pyrimidine using peracetic acid 40%. Further on reacting the above mentioned compound with ethyl oxalyl chloride at 0-5°, 4-[Para-methyl phenoxy]-2,6-bis (ethyl oxalyl amino)-pyrimidine-1-oxide was found.

See Scheme V.

Scheme V



Examples

The following examples will furnish further illustrations of the synthesis. All temperatures are reported in degree centrigrade. The elemental analyses are within ± 0.4% of theory unless otherwise stated. The melting points are not corrected. All N → O compounds gave a positive test with ferric chloride solution.

Example 1

Preparation of 4-(1,2,3,6-Tetrahydro-1-pyridyl)-2,6-bis(ethyl oxamyl) pyrimidine-1-oxide. A 0.5 g (0.0024 mol), sample of 2,6-diamino-4 (1,2, 3,6-Tetrahydro-1-pyridyl) pyrimidine-1-oxide was suspended in (2.4 mmol), a solution of 15 ml of methylene chloride containing 1.5 ml of pyridine. The mixture was cooled to 5° and 1-3 ml (0.012 mol) of ethyl oxalyl chloride was added dropwise to the suspension and stirred. The reaction occurred instantaneously and a yellow precipitate deposited. The precipitate was collected on a filter, washed several times with an aqueous solution of sodium bicarbonate, and separated. The organic phase was then dried, concentrated in vacuo, and 10 ml of hexane was added to precipitate a bright yellow compound which was recrystallized from methylene chloride affording 0.54 g, (56.1%) of the product.

Melting point (194-195°) $C_{17}H_{21}N_5O_7$

C:H:N:O 50.1:5.15:17.1:27.5

Example 2

Preparation of 4-(Piperidinyl)-2,6-bis (ethyl oxamyl)-pyrimidine 1-oxide. A solution of 1.0 g (0.4 mmol) Minoxidil in 15 ml methylene chloride and containing 7 ml of pyridine, was treated with 5 ml (0.04 mol) ethyl oxalyl chloride added over a period of 10 minutes at 0°. The mixture was washed with a solution of sodium bicarbonate and the organic phase was then separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Upon addition of a mixture of toluene (3 ml) and hexane (5 ml), a precipitate was deposited and then collected on a filter and dried under reduced pressure to give 1.16 g (56%) of the title compound of melting point 165-168°.

C:H:N:O 49.8:5.62:17.1:27.3

Similar reactions were conducted on 2,6-diamino-4-(morpholinyl)-pyrimidine 1-oxide, 2,6-diamino-4-(pyrrolidinyl)-pyrimidine-1-oxide, 2,6-diamino-4(p-methyl phenoxy)pyrimidine-1-oxide, and was treated with an excess of ethyl oxalyl chloride 4-(morpholinyl)-2,6 bis(ethyl oxamyl) -pyrimidine-1-oxide, which respectively afforded, with the melting point of 182-184°, C:H:N:O 46.7:5.10:17.0:31.1, $C_{16}H_{21}N_5O_8$, 4-(pyrrolidinyl) -2,6-bis (ethyl oxamyl)-pyrimidine-1-oxide, with a melting point of 222-223°, $C_{16}H_{21}N_5)_7$. C:H:N:O, 48.6:5.3:17.7:28.3, as well as 4-(p-methyl phenoxy)2,6-bis(ethyl oxamyl)-pyrimidine-1-oxide, melting point 172-174°, C:H:N:O 52.6:4.71:13.13:29.5, respectively.

It is noteworthy, that the last compound was synthesized from the parent compound 2,4-diamino-6(p-methylphenoxy)pyrimidine-3-oxide. The parent compound was prepared in the following manner:

a) Preparation of 2,4-Diamino-6-(p-methyl-phenoxy)pyrimidine

A mixture of 54 g (0.5 mole)of p-Cresol, 7.2 g (0.05 mol) of 2,4-diamino-6-chloropyrimidine and 3.5 g of potassium hydroxide was heated at 115-120° for a period of 5 hours. The resulting mixture was cooled slightly at (110°) and subsequently treated with a solution of 14 g of potassium hydroxide in 500 ml of water. Upon addition of 50 ml of ethanol, a solid 6.0 g (57%) was deposited and collected and recrystallized from acetonitrile (melting point = 277-279°).

b) Preparation of 2,4-Diamino-6-(p-methyl-phenoxy)pyrimidine 3-oxide

A mixture of 4.0 g (0.02 mol) of 2,4-diamino-6(p-methyl phenoxy) pyrimidine was suspended in 100 ml of methanol and cooled to 0-5°. A solution of 3.2 g (0.02 mol) of m-chloro perbenzoic acid in 30 ml of methanol and was then added over a period of 15 minutes to the suspension. The resulting mixture was stirred for three hours and the excess solvent removed under reduced pressure. The residue was then dissolved in 50 ml of ethylacetate, and the solution extracted 3 times with 2% aqueous sodium hydroxide. The organic phase was separated, dried and concentrated. Upon cooling to 0°, a precipitate deposit which was collected on filter and air-dried to give 1.9 g (45%) of the oxide, melting point 255-258°.

$C_{11}H_{12}N_4O_2$, C:H:N:O, 56.8:5.17:24.1:13.7

Example 3

Preparation of 2,6-bis(ethyl oxamyl)-4-(pyrrolidinyl)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt. A mixture of 0.5 g (0.2 mmol) of 2,6-diamino-4-(pyrrolidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt in 8 ml pyridine and 15 ml methylene chloride was cooled externally with ice. 2 ml (10.01 mol) of cold ethyl oxalyl chloride was added dropwise to the mixture. The reaction occurs instantly, with a yellow precipitate immediately forming. The resulting mixture was collected on a filter, washed several times with an aqueous solution of sodium bicarbonate and separated. The organic phase was then dried, concentrated and crystallized from toluene which afforded 0.6 g (65%) of a yellow product.

Example 4

Preparation of 2,6-bis(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt. A mixture of 0.2 g (0.4 mmol) of 4-(piperidinyl)2,6-bis(ethyl oxamyl)-pyridine-1-oxide and 0.4 g (0.2 mmol) of sulfur trioxide pyridine complex in 10 ml of dimethyl formamide (DMF) and was stirred at room temperature for a period of 4 hours. The organic phase was then dried, concentrated in vacuo, and hot acetonitrile was added to the residue to precipitate a bright yellow compound. The solid was washed with water and then washed repeatedly with ether. The yield was 0.07 g (28%), affording a bright yellow compound.

Example 5

Preparation of 2,6-bis(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy) pyrimidinium hydroxide, inner salt. A mixture of 1.0 g (0.3 mmol) of 2,6-diamino-4-(piperidinyl)-1(sulfooxy)-pyrimidinium hydroxide, inner salt (Minoxidil sulfate) was dissolved in 20 ml of dimethyl formamide and 3 ml of pyridine in 10 ml of cold methylene chloride was also added to the mixture dropwise. 20 ml of methylene chloride was added and the resulting mixture was washed several times with an aqueous solution of sodium bicarbonate. The methylene chloride layer was then separated, dried and concentrated. The product was then crystallized from hot acetonitrile which yielded 0.5 g (30%) of the product.

Example 6

Preparation of 2,6-bis(ethyl oxamyl)-4-(1,2,3,6-Tetrahydro pyridyl)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt. Following Example 5, and using 2,6-diamino-4(1,2,3,6-Tetrahydro pyridyl)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt and ethyl oxalyl chloride, there was obtained, the title compound.

Example 7

Preparation of 2,6-bis(ethoxy carboxyl amino)-4-(1,2,3,6-Tetrahydro pyridyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt. 0.3 g (0.8 mmol) of 4-(1,2,3,6-Tetrahydro-1-pyridyl)-2,6-bis(ethoxy carbonyl amino)-pyrimidine-1-oxide was dissolved in a mixture of 15 ml of dimethyl formamide and 20 ml of CH_2Cl_2. The resulting mixture was reacted and stirred with 0.6 g (0.3 mmol) of sulfur trioxide pyridine complex at room temperature for a period of 2.5 hours and the excess solvents were removed under reduced pressure. The residue was cooled at 0-5° and was triturated with hot acetonitrile, affording 0.3 g (83%) of a white crystalline substance, with a melting point of 147-148°.

Example 8

Preparation of 2,6-diamino-4-(1-pyrrolidinyl)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt. A mixture of 1 g (0.5 mmol) of 2,6-diamino-4 (1-pyrrolidinyl)-pyrimidine 1-oxide and 1.6 grams (0.01 mol) of sulfur trioxide pyridine complex in 15 ml of dimethyl formamide were stirred at 25° for a period of 2 hours. The precipitate deposit was collected on a filter, washed with water and dried, which gave 1.2 g (86%) of the title compound, with a melting point of 225-227°.

C:H:N:O:S 34.9:4.72:25.4:23.2:11.6

Example 9

Also following Example 8, but using 2,6-diamino-4-(diallylamine)pyrimidine-1-oxide and sulfur trioxide pyridine complex and also reacting 2,6-diamino-4-(1,2,3,6-Tetrahydro-1-pyridyl)pyrimidine-1-oxide with sulfur trioxide pyridine complex in dimethyl formamide, there were obtained respectively 2,6-diamino-4-(diallylamine)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt with the melting point of 174-175° and 2,6-diamino-4-(1,2,3,6-tetra hydro-1-pyridyl)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt with the melting point of 207-209°.

Example 10

Preparation of 4-(pyrrolydinyl)-2,6-bis(ethoxy carbonyl amino)-pyrimidine -1-oxide

A mixture of 1.0 g (0.5 mmol) of 2,6-diamino-4-(pyrrolydinyl)-pyrimidine-1-oxide in 15 ml methylene chloride containing 2 ml of pyridine was stirred and cooled in ice-bath. Ethyl chloroformate, 2.5 ml (0.02 mol) was added over a period of 15 minutes at 0°. The mixture was stirred for ½ hour in 0-5°C, and then over night at room temperature. The precipitate was washed with water, the organic phase was separated, dried and concentrated which afforded 1.2 g (70%) of a solid with the melting point of 155-157°. C:H:N:O 49.5:6.1:20.6:23.5

Example 11

Preparation of 2,6-bis(ethoxy carbonyl amino)-4-(pyrrolidinyl)-1-(sulfooxy) -pyrimidinium hydroxide inner salt

0.6 g (0.1 mmol) of 4-(pyrrolidinyl)-2,6-bis(ethoxy carbonyl amino)-pyrimidine-1-oxide and 1 g (0.006 mol) of sulfur trioxide pyridine complex were reacted at room temperature in 10 ml of dimethyl formamide (DMF). The mixture was stirred overnight which afforded a precipitate. The solvent was removed under reduced pressure. The residue was cooled in an ice bath and crystallized from hot acetonitrile, affording 0.7 g (95%) of a white crystalline substance with a melting point of 165-167°.

C:H:N:O 40.0:5.01:16.7:30.5:7.63

Example 12

Preparation of 4-(diallylamino)-2,6-bis(ethoxy carbonyl amino)-pyrimidine-1-oxide

1 g (0.004 mol) of 2,6-diamino-4-(diallylamino)-pyrimidine-1-oxide was suspended in 15 ml methylene chloride and cooled at 0-5°. 1.8 ml (0.022 mol) of pyridine was added to the suspension. Cold ethyl chloroformate, 2.1 ml (0.022 mol) was added dropwise over a period of ten minutes. The mixture was stirred for ½ hour at 0-5°C, and then washed several times with water (30 ml). The organic layer was dried and concentrated under reduced pressure which afforded 1.2 g (73%) of a white crystalline solid with the melting point of 134-135°. C:H:N:O 52.6:6.30:19.1:21.9

Example 13

Preparation of 2,6-bis(ethoxy carbonyl amino)-4-(diallylamino)-1-(sulfooxy)-pyrimidinium inner salt

100 mg (0.27 mmol) of 4-diallylamino-2,6-bis(ethoxy carbonyl amino)-pyrimidine-1-oxide, and 200 mg (1.2 mmol) of sulfur trioxide pyridine complex were dissolved in 10 ml dimethyl formamide (DMF) and stirred at room temperature overnight. Dimethyl formamide was removed under reduced pressure. The residue was cooled at 0-5° and was triturated with hot acetonitrile, affording 95 mg (79%) of a white compound, with a melting point of 150-152°. C:H:N:O 43.1:5.16:15.7:28.7:7.19

Example 14

Preparation of 4-O-tosylyl-2,6-bis-(ethyl oxamyl)-pyrimidine-1-oxide

1 g (3.3 mmol) of 2,4-diamino-6-O-tosylated pyrimidine-3-oxide was suspended in 30 ml of methylene chloride containing 2 ml of pyrimidine. The mixture was stirred and cooled at 5° and 2 ml (16.8 mmol) of ethyl oxalyl chloride was added dropwise over a period of ten minutes. A yellow-orange solution was formed which on further stirring, yielded a yellow precipitate. The precipitate was washed several times with a solution of sodium bicarbonate. The organic phase was separated, dried, and concentrated, affording a yellow precipitate.

Using the method of the examples given above, and starting with the appropriate 3-oxide, all of the compounds of this invention are synthesized.

The pyrimidine oxides and salts of general Formula I or specific Formulas II through V, and pharmaceutically active inner salts thereof, have potent perpherial vasodilating properties, and are, therefore, useful in causing vasodilation. They are orally, topically and parenterally active. Standard pharmacological tests can be employed to demonstrate the vasodilation, particularly the use of Lazer Doppler Veloximetry. The desirable vasodilation is obtained with no adverse toxicity. (See Table I)

It is the object of the present invention to provide improved compositions which are effective in increasing the rate of hairgrowth on mammalian skin.

It is also an object of this invention to provide such improved compositions in combination with retinoids and/or prostacyclin analogues for topical applications to mammalian skin in order to stimulate or improve the rate of hair growth thereon and to prolong the anagen phase of the hair cycle.

It is a further object of this invention to provide such compositions which can be administered topically through encapsulation in a polymeric structure.

Table 1. Effect of compounds on vasodilation as measured by Laser Doppler* flow meter for microvascular perfusion in male rats (hypotrichotic)

Compound	Dose	Z Change	Area	Time (Hours)
#900	60 micrograms per kilogram	+15	Head	1
		+25		2
		+20		4
		+20		24
#907		+50		1
		+40		2
		+50		4
		+40		24
#909		+35		1
		+30		2
		+38		4
		+60		24
#1001		+20		1
		+15		2
		+30		4
		+25		24
#1005		+5		1
		+25		2
		+30		4
		+5		24
#1009		+50		1
		+15		2
		+30		4
		+15		24
#903		+15		1
		+10		2
		+10		24

900 = Minoxidil Sulfate

907 = 4-(morpholino)-2,6-bis(ethyl oxamyl)-pyrimidine-1-oxide

909 = 4-(pyrrolidinyl)-2,6-bis(ethyl oxamyl)-pyrimidine-1-oxide

1001 = 4-(1,2,3,6-tetrahydro-1-pyridyl)-2,6-bis(ethyl oxamyl)-pyrimidine-1-oxide

1005 = 2,6-diamino-4(pyrrolidinyl)-1-(sulfooxy)-pyriminium hydroxide, inner salt

1009 = 2,6-diamino-4(1,2,3,6-tetra hydro-1-pyridyl)-1-(sulfooxy)-pyrimidinium hydroxide, inner salt

903 = 4-(piperidinyl)-2,6-bis(ethyl oxamyl)-pyrimidine-1-oxide

* - Laser Doppler, Perimed Co., SWEDEN

Hairgrowth Data

A rodent model of hypotrichosis has been developed. This variant is useful as an animal model of androgenetic alopecia. The variant displays all the characteristics of male pattern alopecia in humans.

Extreme hair loss is developed after puberty in males. It is typified by initial hair loss on the crown of the head, continuing to the development of hypotrichosis in these animals, as shown by fewer and smaller hair follicles and greatly enlarged sebaceous glands, especially over the crown of the head and the shoulders and upper back. The limbs tend to remain hairy. The females eventually develop male pattern alopecia but not to the same degree as the males.

On subcutaneous implantation of a pellet of the active compounds a decrease in hair loss was observed. A significantly prolonged anagen phase of the hair cycle was observed, associated in a dose response fashion with the uptake of the implanted substance.

An increased rate of hair growth is also associated with the administration of the active compounds, as measured by microscopic measurement of the outgrowth of hair after bleaching or dying.

The term "topical" as employed herein, relates to the use of a compound of the formulas, incorporated in a suitable pharmaceutical carrier, particularly the encapsulation process, and applied at the site of baldness for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by contact with the skin surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, lotions, pastes, jellies, sprays, aerosols, and the like. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases; e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

The percentage by weight of the compound of the formulas herein utilized ranges from about 0.1% to about 20.0% of the pharmaceutical preparations; the aforesaid pharmaceutical carrier for topical application constitutes a major amount of the said preparation.

While the following examples describe the manner and process of making and using the invention and set forth the best mode contemplated by the inventor of carrying out the invention but are not to be construed as

limiting.

Improved Method of Applying the Compounds of the Instant Inven ion:

The preferred method of applying the compounds of this patent to the skin involves entrapment of the compounds of the instant invention within a syneresis-free hydrophobic polymeric network. The active ingredients are either dissolved or dispersed in the monomer mix and in-situ polymerized. The advantages to be derived are the ability to control the release of the active compounds and the ability to protect the active ingredients from non-specific hydrolysis due to the environmental conditions of contact with the applicant vehicle and with the skin.

Amongst several available systems, the Polymer entrapment systems, such as Polytrap by Wicken Products, N.Y., are useful for this purpose.

Examples

Most emollients will provide a good plasticizer for the hydrophobic polymeric lattice, and an emollient base is excellent as a vehicle to apply the active ingredients of the formulation.

The active substrate is converted into a free flowing bead formulation by entrapment with a syneresis-free polymeric network which is hydrophobic. Loading as great as 60-80% should be achieved within the polymeric lattice. In this matrix the functional hair growth agent is held by microsorption and protected from hydrolysis and other modes of decomposition providing prolonged shelf-life and in a form superior to an emulsion.

In this manner it is possible to hold the functional materials under controlled conditions for availability on demand. This system offers the advantage that retinoids, see PCT U.S. 82/01593 can be incorporated as additional functional materials, within a similar polymeric network.

The structural integrity of the polymer matrix can be disrupted by mechanical stress or force such as rubbing on application to produce continuous film of the released active component. This protection is particularly important when one or more of the active ingredients has a short half-life, in the absence of encapsulation and upon release.

An example of these entrapment systems for topical applications of the compositions is the Polytrap system of Wicken Products, N.Y.

The following Examples illustrate the applicant vehicles for the present invention. The methods of administration may vary by lotion, cream, ointment, polymeric beadlets, supplement to chow, coating for seeds, etc. These Examples are only meant to be illustrative and do not limit the mode of administration nor the ingredients which can be admixed to the present invention, nor the amounts which may be used.

Example I

Lotion formulation for the topical administration	% wt to wt
Active ingredients:	
I. All-trans retinoid acid	0.1
II. Compound A*	3.0
Ethanol	q.s to 100.0
Propylene glycol	5.0
Butylated hydroxytoluene	0.1
Safflower oil	1.0
- tocopherol acetate	0.5
Stabilizer	0.1

Example II

Cream conditioner for Topical Administration		
Active ingredients:		
I. All-trans retinoid acid	1.0	(entrapped in polymeric beadlets)
II. Compound A*	10.0	
Distilled water	q.s. to 100	
Cetrimonium Chloride	5.0	
Cetyl alcohol	4.0	
Ethanol	4.0	
Butylated hydroxytoluene	1.0	
Hydrolized animal protein	0.5	
Methylparaben, propylparaben	0.1	
Stabilizer	0.1	

* bis-2,6-(ethyloxamyl)-4-(pyrrolidinyl)-pyrimidine-1-oxide

Example III

All-trans retinoid acid 0.1 gram and 10 grams of Compound A are dissolved in 100 ml of acetone, and the solution admixed with 900 g of USP grade hydrophilic ointment to a uniform consistency; one gram of butylated hydroxy-toluene is added. The water washable cream ointment thus prepared consists of 0.1% retinoic acid and 10% of Compound A.

Example IV

Polymeric Beadlets for topical administration	
Compound A	1 gram
Active ingredients all-trans retinoic acid and	
Compound A entrapped in a acrylates copolymer	25 mg.
Emolient Base	100 ml.

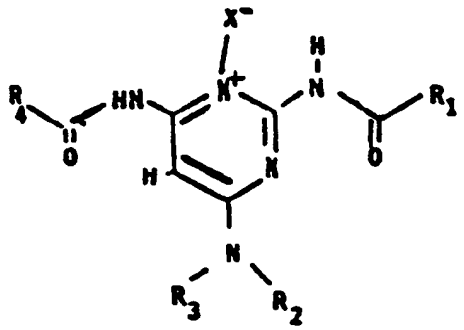
The active ingredients are entrapped within the polymer. The hydrophobic polymer is plasticized by most entrapped ingredients. The degree of plasticization determines whether the beads are soft, spreadable and film forming with minimal pressure or hard with the ability to withstand shearing, of light intensity.

The unexpected novel advantages to be gained from the use of the instant invention are: improved solubility and improved stability and activity of active compounds through increased dispersion of charge; longer action of compounds; excellent penetration of skin due to the lipophilic substituents; and compatibility of compounds with non-polar solvents useful for the preservation of the polar groups while in contact with the skin and useful for the encapsulation of the compounds within a syneresis-free hydrophobic polymeric network.

CLAIMS

I claim:

1.) Substituted pyrimidine oxides useful for increasing the rate of hair growth and prolonging the anagen phase of the hair cycle, comprising compounds of the following formula:



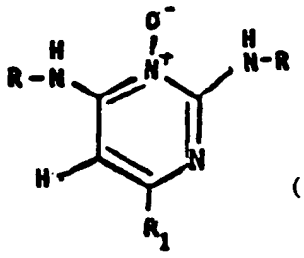
wherein,

a) R_1 and R_4 are alkoxy

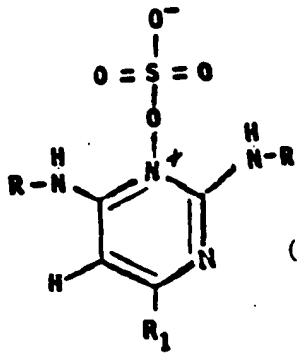
b) R_1 and R_4 = alkoxyacyl groups, such as $-\overset{O}{\overset{\|}{C}}-O-R_5$ where the alkoxy R_5 moiety is derived from lower alcohols,

c) R_2 and R_3 consist of lower alkyl substituents or hydrogen which may be the same or different, with the restriction that if R_2 is hydrogen, R_3 is neither hydrogen or methyl or the reverse; R_2 and R_3 can be alkenyl of 3 to 8 carbon atoms, cyclo alkyl groups incorporating 3 to 8 carbon atoms or phenylalkyl in which the alkyl moiety consists of 1 to 3 carbon atoms as well as R_2 and R_3 linked to form heterocyclic groups including the following: 1-pyrrolidinyl, 1-tetrahydropyridyl, 3-pyrrolidyl, aziridinyl, azetidinyl, piperidino, hexahydroazepinyl, heptamethylenemino, octamethylenimino, thiomorpholino, morpholino, 4-lower-alkyl-piperazinyl, and optionally bearing 1 to 3 alkyl groups including methyl, ethyl, n-propyl and 2-propyl and butyl, and where X is oxide group O^- or OSO^-_3,

2.) A process for the preparation of compounds of the general formula:

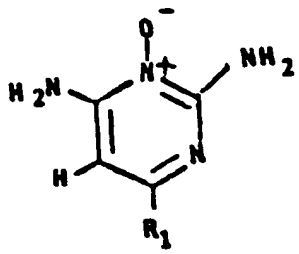


(I)



(II)

wherein R = $\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-OR_3$ or R = $\overset{O}{\overset{\|}{C}}-O-R_3$, where R_3 is a lower alkyl such as methyl, ethyl, propyl, butyl and wherein R_1 is a heterocyclic moiety such as pyrrolidino, morpholino, piperidino, diallylamine or tetrahydropyridyl, thiomorpholine or R_1 is diallylamino or R_1 is a substituted phenol or an O-Tosyl group, which comprises reacting compounds of the formula:



with an alkyl oxalyl halide or an alkyl haloformate and optionally reacting the resultant compound with a latent sulfur source such as sulfur trioxide pyridine complex and sulfur trioxide triethylamine.

3.) A composition useful for increasing the rate of hair growth on mammalian skins, prolonging the anagen phase of the hair cycle and for treating various types of alopecias, comprising an effective amount of a compound selected from the series of Claim 1 and including:

6-amino-2-(ethyl oxamyl)-4-(thiomorpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(pyrrolidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(1,2,5,6-tetra hydro pyridyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(p-methyl-phenoxy)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(O-tosylyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

2-amino-6-(ethoxy carbonyl amino)-4-(pyrrolidinyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(p-methyl phenoxy)-pyrimidine-1-oxide

2-amino-6-(ehoxy carbonyl amino)-4-(diallyalamino)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(morpholinyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(thiomorpholinyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(O-tosylyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(piperidinyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(1,2,5,6-tetra hydro pyridyl)

bis-2,6(ethyl oxamyl)-4-(diallylamino)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis 2,6(ethyl oxamyl)-4-(pyrrolidinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(thiomorpholinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(morpholinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(piperidinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(p-methyl-phenoxy)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(diallylamino)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(pyrrolidinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(O-tosylyl)-pyrimidine-1-oxide

6-amino-2-(ethoxy carbonyl amino)-4-(piperidinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(diallylamino)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(1,2,5,6-tetrahydropyridyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(thiomorpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(morpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(pyrrolidinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(pyrrolidinyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(p-methyl phenoxy)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(diallylamino)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(1,2,5,6-tetrahydropyridyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(piperidinyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(morpholinyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(thiomorpholinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(piperidinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(diallylamino)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(1,2,5,6-tetrahydropyridyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino-4-(morpholinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(thiomorpholinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(pyrrolidinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6-(ethyloxamyl)-4-(piperidinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(p-methyl-phenoxy)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(diallylamino)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(1,2,5,6-tetrahydropyridyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(morpholinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(thiomorpholinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(pyrrolidinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(O-tosylyl)-pyrimidine-1-oxide

bis-2,6(ethyl oxamyl)-4-(1,2,5,6-tetrahydropyridyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(thiomorpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(morpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(p-methyl phenoxy)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(pyrrolidinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(p-methyl phenoxy)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(1,2,5,6-tetra-hydropyridyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(morpholinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(thiomorpholinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(piperidinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(diallylamino)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(pyrrolindinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(morpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(thiomorpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(1,2,5,6-tetra hydro pyridyl)-1-(sulfooxy-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(diallylamino)-4-(pyrrolidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(p-methyl-phenoxy)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(diallylamino)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(morpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

4.) A composition useful for improving the rate of hair growth on mammalian skins which comprises topically applying to the skin an effective amount of a compound selected from the group consisting of retinoids and retinoid analogs and/or prostacyclin analogues in combintaion with the compounds described in Claims 1 and 3.

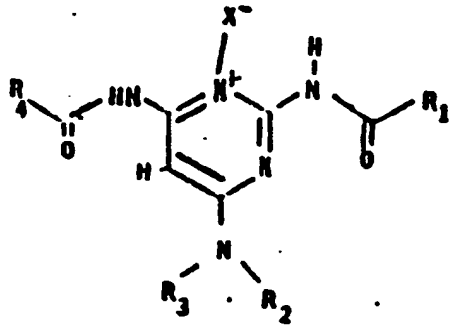
5.) A composition of Claim 4 wherein the retinoid is selected from the group consisting of stereoisomers of vitamin A acid as well as the aldehydes, alcohols, esters, amides, ethers and salts of said compounds, or a retinoid analog, such as those listed in PCT U.S. 82/01593.

6.) A process for applying the compounds of Claims 1,3, and 4 to the skin, which consists of individual encapsulation of the compounds in a syneresis free, hydrophobic, polymeric network, the active ingredients are either dissolved or dispersed in the monomer mix and in-situ polymerized.

AMENDED CLAIMS

[received by the International Bureau on 29 October 1985 (29.10.85); original claim 6 cancelled; claims 1-5 amended (16 pages)]

1.) Substituted pyrimidine oxides useful for increasing the rate of hair growth and prolonging the anagen phase of the hair cycle, comprising compounds of the following formula:



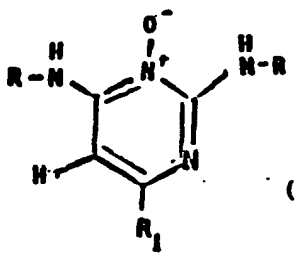
wherein,

a) R_1 and R_4 are alkoxy

b) R_1 and R_4 = alkoxyacyl groups, such as $-C-O-R_5$ where the alkoxy R_5 moiety is derived from lower alcohols,

c) R_2 and R_3 consist of lower alkyl substituents or hydrogen which may be the same or different, with the restriction that if R_2 is hydrogen, R_3 is neither hydrogen or methyl or the reverse; R_2 and R_3 can be alkenyl of 3 to 8 carbon atoms, cyclo alkyl groups incorporating 3 to 8 carbon atoms or phenylalkyl in which the alkyl moiety consists of 1 to 3 carbon atoms as well as R_2 and R_3 linked to form heterocyclic groups including the following: 1-pyrrolidinyl, 1-tetrahydropyridyl, 3-pyrrolidyl, aziridinyl, azetidinyl, piperidino, hexahydroazepinyl, heptamethyleneimino, octamethyleniminо, thiomorpholino, morpholino, 4-lower-alkyl-piperazinyl, and optionally bearing 1 to 3 alkyl groups including methyl, ethyl, n-propyl and 2-propyl and butyl, and where X is oxide group O^- or OSO^-_3,

2.) A process for the preparation of compounds of the general formula:



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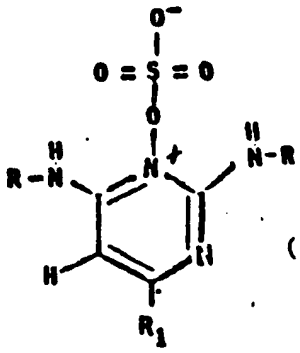
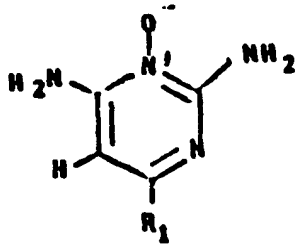


(II)

wherein R = $\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-OR_3$ or R = $\overset{O}{\overset{\|}{C}}-O-R_3$, where R_3 is a lower alkyl such as methyl, ethyl, propyl, butyl and wherein R_1 is a heterocyclic moiety such as pyrrolidino, morpholino, piperidino, diallylamine or tetrahydropyridyl, thiomorpholine or R_1 is diallylamino or R_1 is a substituted phenol or an O-Tosyl group, which comprises reacting compounds of the formula:



with an alkyl oxalyl halide or an alkyl haloformate and optionally reacting the resultant compound with a latent sulfur source such as sulfur trioxide pyridine complex and sulfur trioxide triethylamine.

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3.) A composition useful for increasing the rate of hair growth on mammalian skins, prolonging the anagen phase of the hair cycle and for treating various types of alopecias, comprising an effective amount of a compound selected from the series of Claim 1 and including:

6-amino-2-(ethyl oxamyl)-4-(thiomorpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(pyrrolidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(1,2,5,6-tetra hydro pyridyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(p-methyl-phenoxy)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(O-tosylyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

2-amino-6-(ethoxy carbonyl amino)-4-(pyrrolidinyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(p-methyl phenoxy)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(diallylamino)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(morpholinyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(thiomorpholinyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(O-tosylyl)-pyrimidine-1-oxide

2-amino-6-(ethoxy carbonyl amino)-4-(piperidinyl)-pyrimidine-1-oxide

bis-2,6(ethyl oxamyl)-4-(diallylamino)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis 2,6(ethyl oxamyl)-4-(pyrrolidinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(thiomorpholinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(morpholinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(piperidinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(p-methyl-phenoxy)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(diallylamino)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(pyrrolidinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(O-tosylyl)-pyrimidine-1-oxide

6-amino-2-(ethoxy carbonyl amino)-4-(piperidinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(diallylamino)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(1,2,5,6-tetrahydropyridyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(thiomorpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(morpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethoxy carbonyl amino)-4-(pyrrolidinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-amino-2-(ethyl oxamyl)-4-(pyrrolidinyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(p-methyl phenoxy)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(diallylamino)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(1,2,5,6-tetrahydropyridyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(piperidinyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(morpholinyl)-pyrimidine-1-oxide

6-amino-2-(ethyl oxamyl)-4-(thiomorpholinyl)-pyrimidine-1-oxide

bis-2,6(ethoxy carbonyl amino)-4-(piperidinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(diallylamino)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(1,2,5,6-tetrahydropyridyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2;6(ethoxy carbonyl amino-4-(morpholinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(thiomorpholinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6(ethoxy carbonyl amino)-4-(pyrrolidinyl)-1-(sulfooxy) pyrimidinium hydroxide inner salt.

bis-2,6-(ethyloxamyl)-4-(piperidinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(p-methyl-phenoxy)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(diallylamino)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(1,2,5,6-tetrahydropyridyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(morpholinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(thiomorpholinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(pyrrolidinyl)-pyrimidine-1-oxide

bis-2,6-(ethyloxamyl)-4-(O-tosylyl)-pyrimidine-1-oxide

bis-2,6(ethyl oxamyl)-4-(1,2,5,6-tetrahydropyridyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(thiomorpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(morpholinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

bis-2,6(ethyl oxamyl)-4-(p-methyl phenoxy)-1-(sulfooxy)pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(pyrrolidinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(p-methyl phenoxy)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(1,2,5,6-tetra-hydropyridyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(morpholinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(thiomorpholinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(piperidinyl)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(diallylamino)-pyrimidine-1-oxide

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(pyrrolindinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(morpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(thiomorpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(piperidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(1,2,5,6-tetra hydro pyridyl)-1-(sulfooxy-pyrimidinium hydroxide inner salt.

6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(diallylamino)-4-(pyrrolidinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

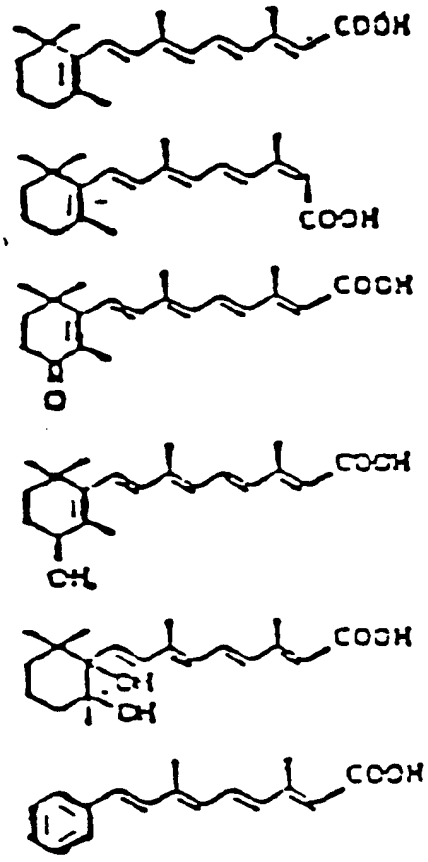
6-(ethoxy carbonyl amino)-2-(ethyl oxamyl)-4-(p-methyl-phenoxy)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

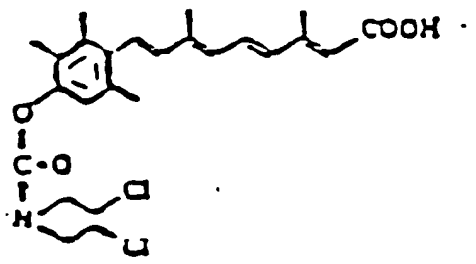
6-amino-2-(ethyl oxamyl)-4-(diallylamino)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

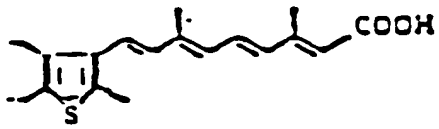
6-amino-2-(ethyl oxamyl)-4-(morpholinyl)-1-(sulfooxy)-pyrimidinium hydroxide inner salt.

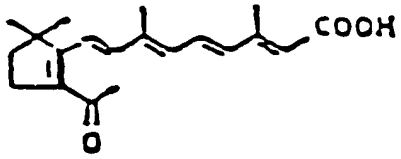
4.) A composition useful for improving the rate of hair growth on mammalian skins which comprises an effective amount of a compound selected from the group consisting of retinoids and retinoid analogs and/or prostacyclin analogues in combination with the compounds described in Claims 1 and 3.

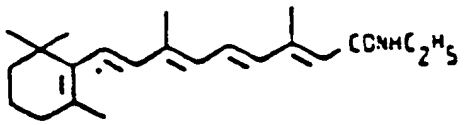
5.) A composition of Claim 4 wherein the retinoid is selected from the group consisting of stereoisomers of vitamin A acid as well as the aldehydes, alcohols, esters, amides, ethers and salts of said compounds, or a retinoid analog, such as those isted in PCT U.S. 82/01593, and including, but not limited to, the following retinoids:



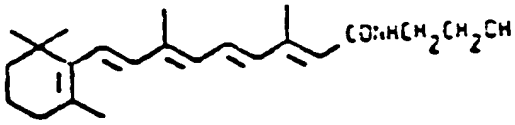




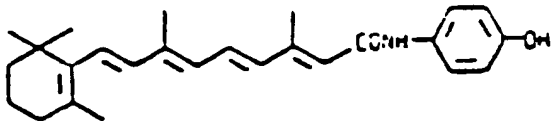


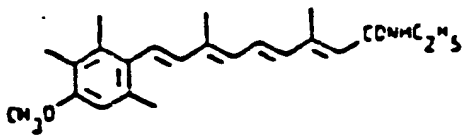


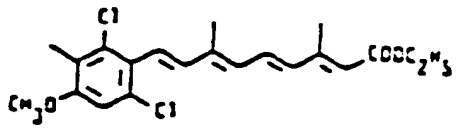
Retinoic Acid Ethyl Amide



Retinoic Acid 2-Hydroxyethyl Amide







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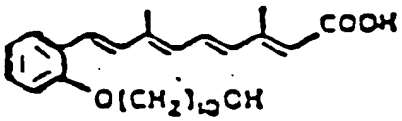
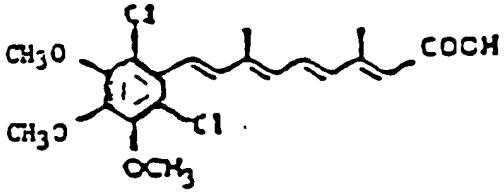
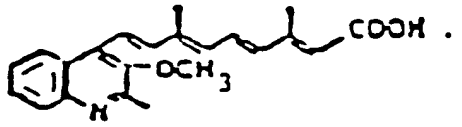
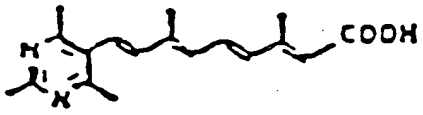
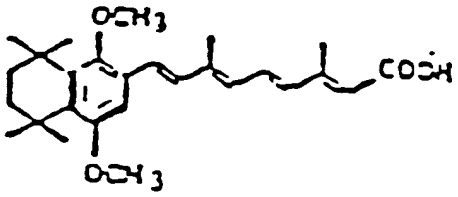
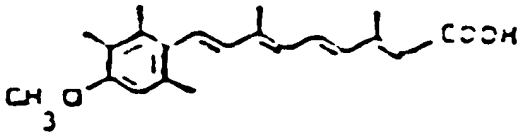


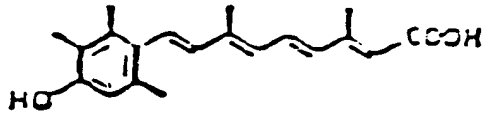


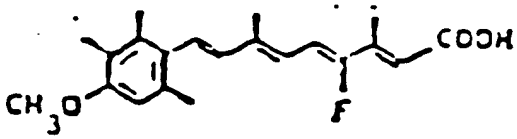


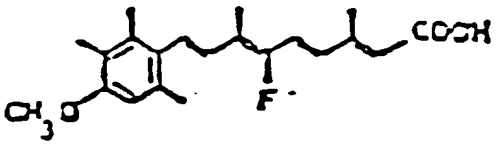




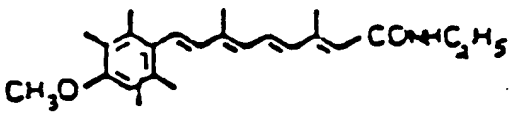




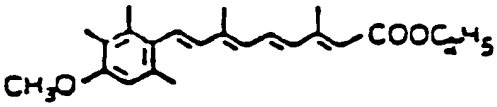




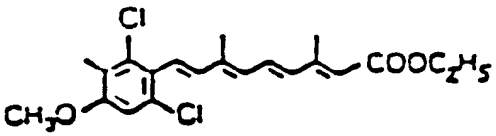
Trimethylmethoxyphenyl (TMMP) analog of retinoic acid ethyl amide (Motretinid)



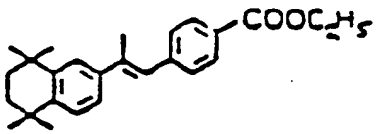
Trimethylmethoxyphenyl (TMMP) analog of retinoic acid ethyl ester (Etretinate)



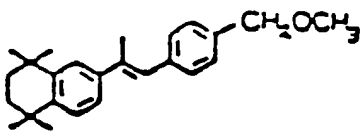
Dichloromethylmethoxyphenyl (DCMMP) analog of retinoic acid ethyl ester



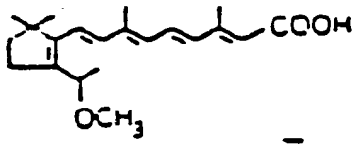
Arotinoid ethyl ester

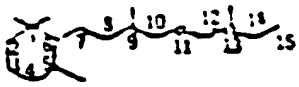


Arotinoid methyl ether

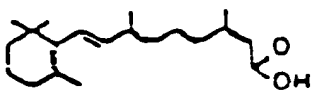


1-Methoxyethyl-cyclopentenyl analog of retinoic acid

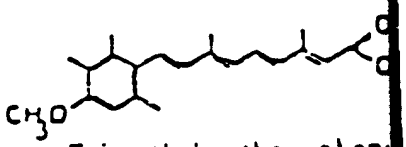




Axerophthene

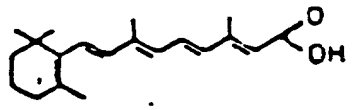


13-*cis*-Retinoic acid

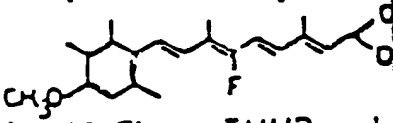


Trimethylmethoxyphenyl (TMMP) analog of RA

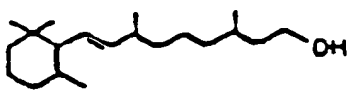
Retinol



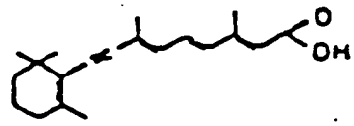
9-*cis*-all-*trans*-Retinoic acid (RA)



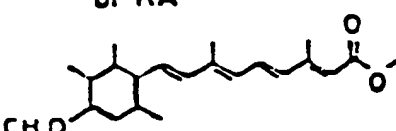
10-Fluoro-TMMP analog of RA



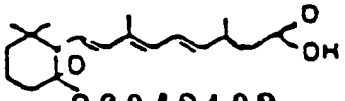
Retinol

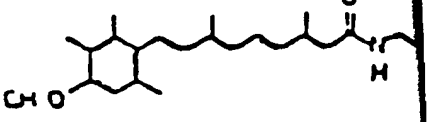


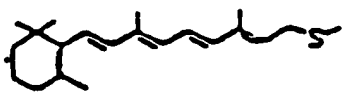
7,8-Dehydro analog of RA



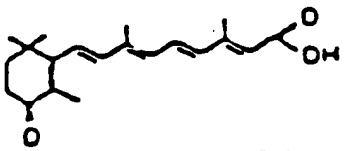
TMMP analog of ethyl retinoate



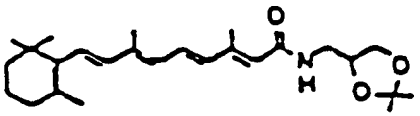




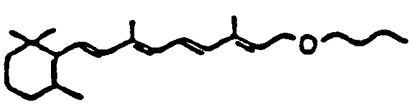
Retinyl methyl thioether



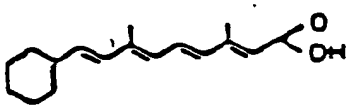
4-Oxo analog of RA



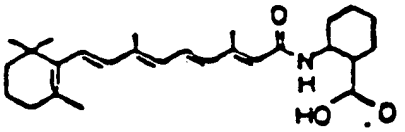
N-Methyl-dimethyldioxolan-retinamide



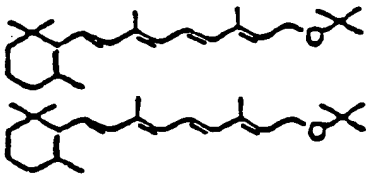
Retinyl n-butyl ether



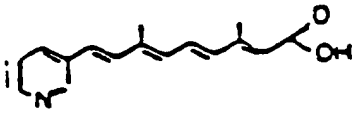
Phenyl analog of RA



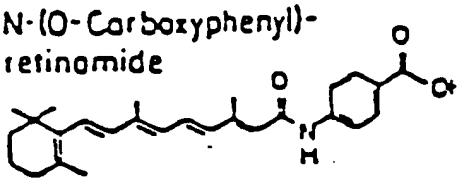
N-(O-Carboxyphenyl)-retinamide



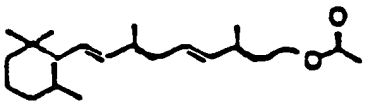
Retinyl *tert*-butyl ether



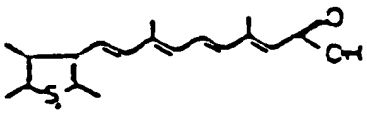
Pyridyl analog of RA



N-(p-Carboxyphenyl)-retinamide

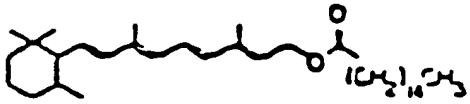


Retinyl acetate

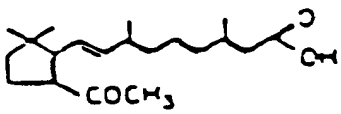


Trimethylthiophene (TMT) analog of RA

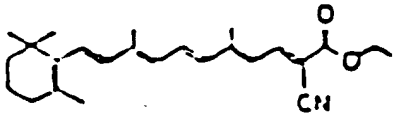
N-Benzoyl-retinylamine



Retinyl palmitate

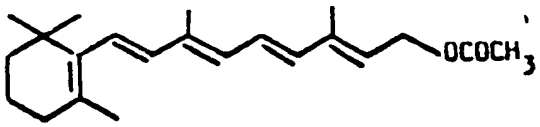


Dimethylacetyl cyclo-

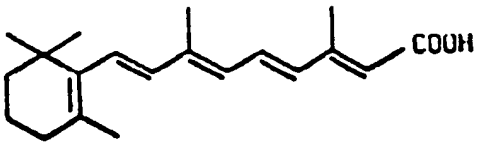


Retinylidene ethylcyano-

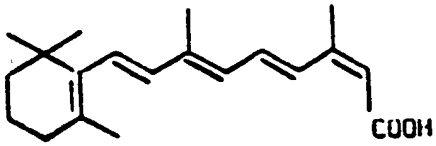
86042103



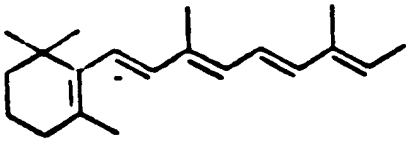
retinyl acetate



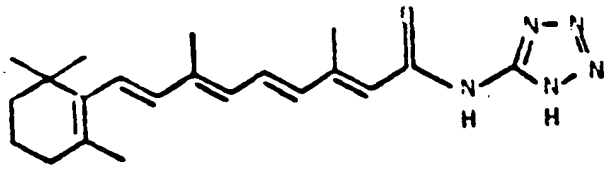
(all-E)-retinoic acid



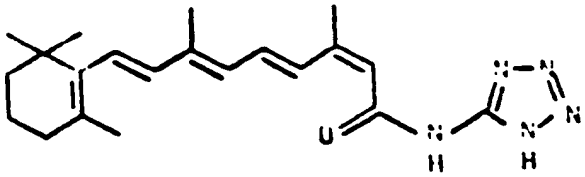
(13 Z)-retinoic acid



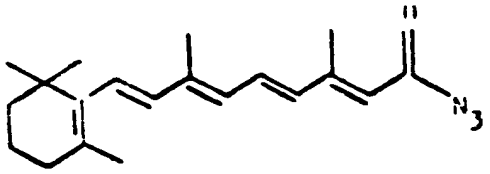
35689 - BASF



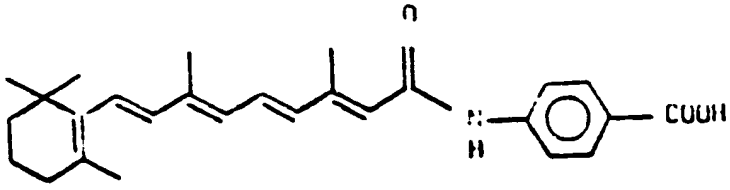
35739 - BASF



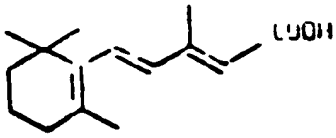
37175 - BASF



36591 - BASF



35681-BASF



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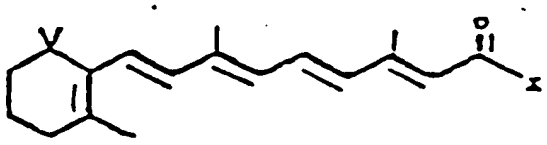
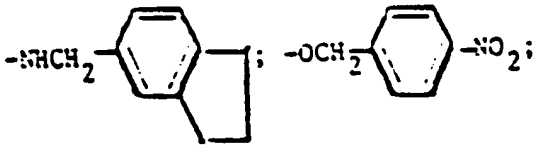
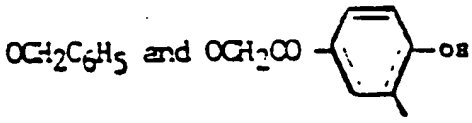
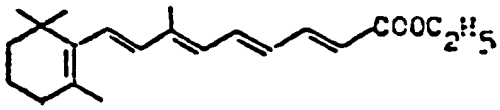
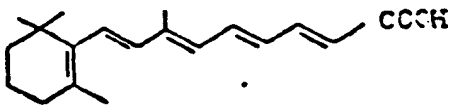
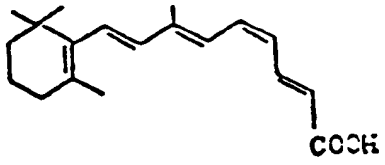
36592 - BASF

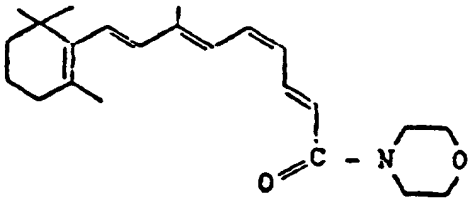
A Retinoid analog 

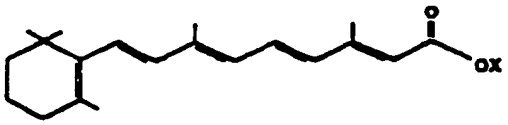
wherein X is a member selected from the group consisting of: $-OCH_2CONH_2$; mixed - $OCH_2CH(OH)CH_3$ and - $OCH(CH_3)CH_2OH$; $-OCH_2CH_2OH$;  ; $OCH_2C_6H_5$ and 



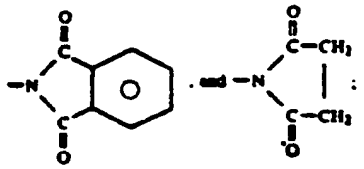


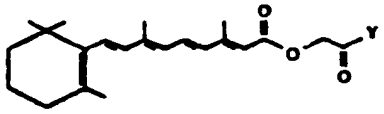




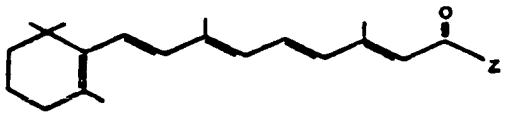


wherein X is a member selected from the group consisting of: 2-cyclohexylethyl; 10-carbomethyoxydecyl; 4-hydroxybutyl; cholesteryl; 4-bromobenzyl;

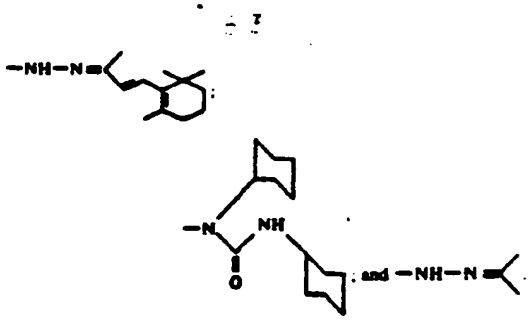




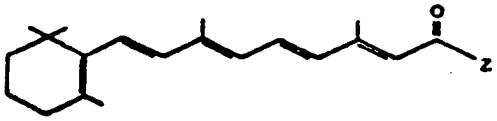
wherein Y is a member selected from the group consisting of; cholesteryl; phenyl; 4-bromophenyl; 4-nitrophenyl; 4-cyanophenyl; and 2,4-dichlorophenyl; amides of all-trans retinoid acid having the following formula:



wherein Z is a member selected from the group consisting of: n-propylamino; tert-butylamino; 1,1,3,3,-tetramethylbutylamino; 4-hydroxyphenylamino; 4-carbomethoxy-3-hydroxyphenylamino; 2-(3,4-dimethoxyphenyl)-ethylamino; 2-benzothiazolylamino; 1-imidazolyl' 1-(2-nicotinoylhydrazolyl); 1-benzotriazolyl; 1-(1,2,4-triazolyl); or Z can be the following:



or



wherein Z is a member selected from the group consisting of: n-propylamino; tert-butylamino; 1,1,3,3-tetramethylbutylamino; 4-hydroxyphenylamino; 4-carbomethoxy-3-hydroxyphenylamino; 2-(3,4-dimethoxyphenyl)-ethylamino; 2-benzothiazolylamino; 1-imidazolyl; 1-(2-nicotinoylhydrazolyl); 1-benzotriazolyl; 1-(1,2,4-triazolyl); or the retinoid can be from the group consisting of N-n-Propyl all-trans-retinamide; N-Tert.-butyl all-trans-retinamide; N-1,1,3,3-Tetramethyl)-butyl all-trans retinamide; N-[-(3,4-Dimethoxyphenyl)ethyl]-all-trans retinamide; N-(4-hydroxyphenyl)-all-trans retinamide; N-(4-carbomethoxy-3-hydroxyphenyl)-all-trans retinamide.

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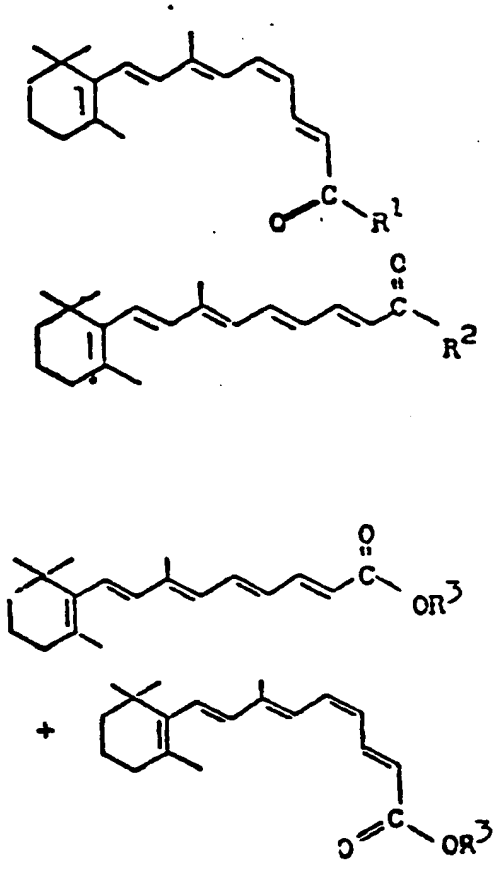

in which R_1, R_2 or R_3 represent hydroxy, alkoxy, phenoxy, amide or carboxylic acid groups, as described in Demande De Brevet D'Invention, No. 75 36850 or Publication Number 2,293,193.

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6.) (Cancelled)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/01329

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL.[4] C07D 239/02, 239/70
U.S. CL. 544/255, 312, 323

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System [5]	Classification Symbols
U.S.	544/255, 312, 323

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category * [15]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 4,150,131 PUBLISHED 17 APRIL 1979 MULLER ET AL	1-3
X	US, A, 4,150,132 PUBLISHED 17 APRIL 1979 MULLER ET AL	1-3
X	US, A, 4,220,772 PUBLISHED 02 SEPTEMBER 1980 MULLER ET AL	1-3
Y	US, A, 4,339,453 PUBLISHED 13 JULY 1982 GRIER ET AL	1-3
X	US, A, 4,360,521 PUBLISHED 23 NOVEMBER 1982 HENGARTNER ET AL	1-3
Y	DE, A, 2 110 111 PUBLISHED 16 SEPTEMBER 1971 SCHALK ET AL	1-3
X	N, The New England Journal of Medicine, issued 26 JULY 1973, Vol. 289, No. 4, Pettinger Et Al, "MINOXIDIL-AN ALTERNATIVE to NEPHRECTOMY for REFRACTORY HYPERTENSION", pp. 167-171.	1-3, 5

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* Special categories of cited documents: [19]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
19 AUGUST 1985	30 AUG 1985

International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	Nathan M. Nutter

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	N, HELVETICA CHIMICA ACTA, issued 11 MAY 1982 Vol. 65, Fasc. 5, Nr. 142, MULLER ET AL, "Regioselective Synthesis of 2-oxo-2,8-dihydro-[1,2,4]-oxadiazolo[2,3-a]pyrimidine-7-carbamates: A New Class of Antihypertensive Peripheral Vasodilators".	1-4, 6
X	N, HELVETICA CHIMICA ACTA, issued 11 MAY 1982 Fasc. 5, Nr. 143, MULLER ET AL "Structure of New 2-oxo-2,8-dihydro-[1,2,4]oxadiazolo-[2,3-a]pyrimidinecarbamates".	1-4, 6
X	N, HELVETICA CHIMICA ACTA, issued 30 NOVEMBER 1982, Vol. 66, Fasc. 2 Nr. 61, MULLER ET AL "Synthesis of 2-Oxo-2H-[1,2,4]oxadiazolo-[2,3-c]pyrimidine-5-carbamates", pp. 669-672	1-4, 6

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ... because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. [X] Claim numbers 5, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

It is improper to refer to material not disclosed in the application or that is referenced to another application. In this case, the claim refers to PCT/US82/01593.

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

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4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.